REMARKS

I. Status of the Claims

Claims 274-283 are pending. Applicants have canceled the remaining claims to simplify issues and expedite prosecution. Minor amendments have been made to claims 274 and 280 to improve clarity. Support is found, for example, in Example 11.

II. Information Disclosure Statement

For several items in the information disclosure statement forms submitted on March 26, 2011, the Examiner failed to initial the boxes confirming that these items were considered. However, all of the relevant information available was supplied in the form in compliance with 37 C.F.R. §1.98. Pursuant to MPEP §609, the Examiner was required to acknowledge consideration of these items, as long as they were submitted in compliance with Rule 98 and during the proper time period under 37 C.F.R. §1.97. Applicants request that the Examiner provide a fully-initialed copy of these forms.

III. Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 233-237 and 239-242 under 35 U.S.C. §112, first paragraph, is mooted by cancellation of the claims in question. Other rejections under 35 U.S.C. §112, first paragraph, were withdrawn in view of the Board's decision in application no. 08/444,790, now U.S. Patent No. 8,063,182.

III. Rejection under 35 U.S.C. §103

The Action maintained the rejection of claims 233-237, 239-243, 246-253, 255-261 and 274-286 as obvious under 35 U.S.C. §103 in view of a variety of combinations of art: (1) Smith et al., U.S. Patent No. 5,395,760 ("Smith Patent"), in view of Capon et al., U.S. Patent No. 5,428,130 ("Capon Patent" or "Capon '130 patent"), (2) Dembic et al., *Cytokine* 2: 231-237, 1990 ("Dembic") in view of the Smith Patent and the Capon Patent, and (3) the Smith Patent, in view of Hohmann et al., *J. Biol. Chem.* 264: 14927-14934, 1989 ("Hohmann") and the Capon Patent.

A. Smith Patent in view of Capon '130 Patent

The Smith Patent was cited for teaching the p75 TNF receptor (TNFR), the extracellular portion of the receptor, and a fusion of "IgG1 [to a] soluble portion of a p75kD TNF receptor wherein the fusion protein is **bivalent** for TNF receptor." Action, p. 8. The Examiner admitted that "Smith et al. do not teach [an IgG fusion protein] wherein the IG portion lacks the first domain of the constant region [CH1]." Action, p. 8. The Capon Patent was then cited for teaching an immunoglobulin (Ig) fusion protein where "the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain." Action, p. 9, citing Capon Patent at col. 10, second paragraph. The Examiner asserted that the combination rendered the claimed invention obvious.

In their prior response, Applicants noted that obviousness had been dispositively addressed by the decision of the Board of Patent Appeals and Interferences in Appeal 2009-014889 (submitted in the Information Disclosure Statement dated March 15, 2011; the "Decision"), which concluded that "Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection." Decision on Appeal at 7. The obviousness rejection in that related case, now U.S. Patent No. 8,063,182, had been based on a similar combination of references: Dembic, like the Smith Patent, had been cited for its disclosure of the p75 TNFR, and the Capon Patent disclosure[1] had been cited for teaching the immunoglobulin portion of Ig fusion molecules that contain a ligand-binding portion of a receptor.

However, the Examiner declined to follow the Board's Decision merely because the exact same combination of references was not before the Board. Applicants respectfully traverse. The present obviousness rejection based upon the Smith Patent and the Capon Patent leads one of ordinary skill even further away from the claimed invention than the combination of references considered by the Board. Therefore, the prior holding by the Board applies with even more force to this present, weaker rejection.

[1] US Patent 5,128,130 (which is currently cited) is a continuation of a continuation of US Patent 5,116,964 (which was cited in the rejection that was the subject of the appeal), and these patents therefore share the same disclosure.

Notably, although the Smith Patent was not discussed in the Decision, it was one of only 5 cited references on pages 2-3 of the Decision in the Board's Statement of the Case. Thus, the Board was aware of the Smith Patent, and could have instituted further rejections of the claims based on this reference. The Board declined to do so. For this additional reason, Applicants submit that the Board's determination in U.S. Patent No. 8,063,182 should be adhered to in the instant case.

Wholly independent of the Board's prior Decision in the related patent, there are multiple reasons why the present obviousness rejection should be withdrawn. First, no proper *prima facie* case of obviousness exists. The Capon Patent disclosure discloses a broad genus of fusion proteins that comprise fragments of immunoglobulins and fragments of ligand-binding proteins. The Capon Patent does not, however, teach the use of a TNF receptor to make such a fusion protein. The Smith Patent discloses the p75 TNFR DNA and amino acid sequences, and it contemplates a wide variety of fragments, conjugates and fusion proteins. Among the conjugates and fusion proteins described in the Smith Patent are a class of "chimeric antibody molecules" that the Examiner asserts are bivalent. The Examiner admits that the Smith Patent does not teach fusion of TNFR fragments to a heavy chain lacking CH1.

The Examiner failed to articulate a rationale prompting one of ordinary skill to select and then modify any of the embodiments of the genus disclosed in Smith in order to reach the claimed invention. There were many reasons to prefer embodiments other than those recited in the claims. Moreover, statements in the cited art itself explicitly discourage the claimed invention.

Second, even if one assumes a *prima facie* case, Applicants' overwhelming evidence of unexpected properties mandates the same conclusion of nonobviousness as in the Board's decision. The Examiner's refusal to consider this evidence of unexpected results, simply because it is not a direct comparison to a hypothetical embodiment arbitrarily selected from only one of the two obviousness references, is reversible error. It is well settled that indirect evidence is permitted and *must* be considered in making a determination of obviousness or nonobviousness. MPEP §716.02(b)(III). When the evidence is properly considered, it is clear that the combination recited in the present claims is "more than the predictable use of prior art elements according to their established functions." MPEP

§2141(I), citing *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007).

1. The asserted prima facie case of obviousness is defective

The asserted *prima facie* case of obviousness is defective for the reasons explained in great detail in the prior response filed March 15, 2011. The Examiner failed to provide a reason to select the class of chimeric antibody molecules described in the Smith Patent from among the many analogs, fusion proteins, conjugates, monovalent and polyvalent forms of TNFR described at cols. 7-10, much less a reason to select the particular bivalent chimeric antibody molecule referenced in the Action. The Examiner further failed to provide a reason or incentive prompting modification of this molecule, which contains two light chains covalently bound to two heavy chains, to remove the light chains and the CH1 domains of the heavy chains. At best, the ordinary skilled artisan reading the two cited references together would select the chimeric antibody molecules described in the Capon Patent that are the same as those described in the Smith Patent – embodiments that are different from those encoded by the claimed nucleic acids and produced by the claimed methods. In particular, the worker of ordinary skill would be deterred from removing the CH1 domains and light chains given the explicit guidance in the Smith Patent to use "unmodified constant domains [emphasis added]".

Similarly, with respect to the Capon Patent, the Examiner failed to provide a rationale for selecting the particular immunoglobulin portion recited in the claims from the over 250 different general formats for Ig/ligand binding protein fusions at cols. 12-14, and the thousands of possible specific fusion proteins, including monomeric, homodimeric, heterodimeric, trimeric, tetrameric, homomultimeric and heteromultimeric forms.

Applicants' response filed May 15, 2011 noted that there were many reasons to prefer fusion proteins other than those recited in the claims. For example, the Capon Patent states that a "preferred embodiment" retains the entire constant region (the ligand binding partner being substituted for the variable region of an antibody, *see* col. 5, ln. 37-41 and col. 15, ln. 9-25). See also Capon at col. 10, lines 9-12. Applicants reminded the Examiner that MPEP §2144.08 requires that such teachings be considered because they "may

weigh against selecting the claimed species or subgenus and thus against a determination of obviousness."

The Action failed to address these teachings in a substantive manner. The Examiner's only response to these arguments was to quote MPEP §2123, suggesting that nonpreferred and alternative embodiments still constitute prior art. Action, p. 9. However, the mere fact that a compound could be made is not a sufficient reason to select it, and the mere fact that a modification might be possible is not an incentive prompting the modification. Here, the chimeric antibody molecule described in the Smith Patent, which was arbitrarily selected by the Examiner as the "lead" compound, was a hypothetical description.

The *prima facie* case is also defective because the Action failed to explain why one of ordinary skill would have ignored the explicit teaching of the Smith Patent that discourages modifying the constant region domains. The chimeric antibody molecules are described as "having unmodified constant region domains." Smith Patent, col. 10, ln. 54-57. An unmodified constant domain of an antibody contains both heavy and light chain sequences and assembles into a very different molecule. The Smith Patent therefore teaches away from the protein encoded by the claimed nucleic acids, which lacks a light chain constant domain and a heavy chain constant domain CH1. Even the section of the MPEP §2123 quoted by the Examiner in the Action supports Applicants' position that a disclosure that "discourage[s] the solution claimed" constitutes a teaching away.

Thus, no proper *prima facie* case of obviousness can be established without a rationale motivating the selection of the class of chimeric antibody molecules described in the Smith Patent, and a reason or incentive prompting modification of these molecules to remove the complete light chain and the CH1 domain, in the face of explicit teachings discouraging such a modification. In the absence of such factual findings and articulated rationale, the obviousness rejection must be withdrawn.

2. Unexpected results require a conclusion of nonobviousness

The present Action also refuses to consider any of Applicants' evidence of unexpected results because (1) they are not a direct comparison to one embodiment, an arbitrarily-chosen hypothetical embodiment that did not even physically exist (Action, p. 12)

and because (2) their practical significance as determined by a correlation to actual *in vivo* function has not been definitively proven (Action, p. 14). This is clear legal error.

Applicants are not required to provide any direct comparative evidence to any particular embodiment. "[A]pplicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." MPEP §716.02(e)(III). Moreover, it is well settled that indirect evidence is permitted and must be considered in making a determination of obviousness or nonobviousness. MPEP §716.02(b)(III).

In looking to the "closest prior art," the Examiner improperly focuses on Smith to the exclusion of Capon. The Action refused to consider evidence regarding CD4-Ig fusions and IL-2-Ig fusions (Action, p. 17) because the evidence was not a comparison to the arbitrary hypothetical "closest prior art" put forward in the Action. But, for purposes of assessing binding affinity and/or effector functions, these molecules from Capon are just as "close" to Applicants' novel combination as would be any of the molecules set forth in Smith. Indeed, for this purpose, the two-chain configuration of these CD4-Ig and IL-2-Ig fusions is **closer** to the fusion protein encoded by the claimed nucleic acids than the four-chain chimeric antibody molecule described by the Smith Patent. This evidence was therefore relevant for establishing the general expectation in the art that Ig fusions would not exhibit the properties of improved binding affinity and/or reduced effector functions. The Action also ignored Applicants' evidence of improved binding affinity and reduced effector function, as well as the kinetic stability and TNF inhibition data in the Declaration of Dr. Lesslauer (Action, p. 18), because they were not a comparison to the single hypothetical from Smith that the Examiner arbitrarily deemed to be the "closest prior art." Indirect evidence, however, must be considered as explained above.

The Action further refused to consider evidence of reduced effector function compared to anti-TNF antibodies (Action, p. 17), because these molecules are "structurally and functionally distinct" from the claimed invention. This evidence, however, was relevant for establishing the general expectation in the art that TNF-binding molecules which retain the hinge, CH2 and CH3 domains would also retain effector functions. This type of evidence is highly relevant to the required findings of "physical or chemical properties and utilities disclosed for the genus" in relation to the scope and content of the prior art under *Graham v. John Deere*. MPEP §2144.08.

Moreover, Applicants provided evidence in the Declaration of Dr. Taruna Arora ("Arora Declaration," submitted as document D15 in the Information Disclosure Statement submitted in this case on March 15, 2011) directly comparing the two-chain p75 TNFR-IgG fusions encoded by the claimed nucleic acids to other two-chain TNFR embodiments. The claimed two-chain TNFR embodiments are closer in configuration to the other two-chain embodiments disclosed in the Arora Declaration than to either the four-chain chimeric TNFR antibody molecule, of the Smith Patent arbitrarily selected by the Examiner or the non-TNFR-Ig fusions of Capon. Yet the Examiner refused to consider the Arora declaration, stating that it was "not germane" because it did not compare the instant invention to the "closest prior art." Action, p. 12. But the real issue here is not the incremental degree to which the expression product of the claims might compare to any randomly selected one of the myriad disparate structures disclosed in Smith and Capon, but whether the results of Applicants' novel combination differ from what one would otherwise have expected from such a combination.

The Arora declaration contains results of a comparison to two different TNFR/Ig fusions (Delta 57 and Protein 3.5D) that are different from the fusion proteins encoded by the claimed nucleic acids only in that they are missing the first five amino acids of the hinge region, including a cysteine involved in disulfide bonding, that they contain a linker between the TNFR and IgG fragments of these fusion proteins, and because they contain less than the entire extracellular region of the TNF receptor. They are similar to the proteins encoded by the claimed invention in that they (1) have the same homodimeric two-chain configuration, (2) are missing a CH1 domain and (3) are missing the light chain. Yet, these homodimers, unlike the embodiments encoded by the claimed invention, retained effector function. This evidence clearly supports a finding that the lack of effector function seen with proteins encoded by the claimed invention was unexpected. Yet the Action at page 12 ignored this evidence.

The Action objected to the use of Delta 57 and Protein 3.5D for a variety of reasons, including the fact that neither of these proteins contain the entire extracellular region. The fact that these proteins retained the expected effector function, however, clearly shows that they retained sufficient TNF-binding activity of the extracellular domain to constitute a fair comparison.

The Action's objections to the Arora Declaration also included a number of questions that are completely irrelevant to the legal question of unexpected results relative to the cited art. For example, the Action includes questions such as whether anti-TNF antibodies that have effector function "have clinical efficacy in diseases that etanercept cannot be used to treat" (page 13 of Action), or whether monovalent Fab fragments that are missing the Fc region and its associated effector functions are useful for treating disease "without side effects associated with Fc receptors or complement" (page 13 of Action). None of these questions provides a reason to doubt the scientific evidence actually provided.

These remarks suggest that the Examiner believes that superiority must be demonstrated in all properties in order to rebut obviousness. To the contrary, a showing of superiority in only one property is sufficient to rebut a *prima facie* showing of obviousness. *In re Chupp,* 816 F.2d 643, 646 (Fed. Cir. 1987).

Similar issues are raised (page 14 of Action) to assert that the practical significance of the unexpected results is "unclear," yet none of these questions provides an actual reason to doubt the practical significance of the evidence. Clearly the observation that etanercept has markedly reduced effector function was thought by researchers to be of practical significance since it was mentioned as potentially significant in several peer-reviewed articles by different groups of researchers. *See, e.g.,* Arora et al., Cytokine 45:124-131 (2009); Furst et al. (2006), *Sem. Arthritis Rheum.* 36(3):159-167 (both of record). The Action does not dispute that the presence of effector functions, which kill cells that express antigen, is undesirable in some circumstances. The fact that effector functions may be desirable in other circumstances (see page 15 of Action) is irrelevant, since not every property of the claimed molecule need be unexpectedly advantageous to rebut obviousness.

The implied requirement to show that effector function "precludes use of anti-TNF antibodies" (page 15 of Action) or have a "clear correlation" to *in vivo* function has absolutely no basis in statute or case law. As stated above, all that need be shown is at least one unexpected and advantageous property as compared to the prior art. A known practical consequence of effector function is the killing of cells that express the ligand to which the Ig fusion binds. Applicants have pointed to peer-reviewed articles suggesting that this observation is of practical significance, with respect to TNF, because it may be reflected in the monocytopenia (low monocyte count) observed in patients following treatment with anti-

TNF antibody infliximab. *See* Furst et al. (2006), *Semin. Arthritis Rheum.* 36:159-167, at page 164 (Document D2 on SB/08 filed March 29, 2011). It is notable that data suggest that patients treated with infliximab (Remicade®) have elevated risk of reactivation of granulomatous infections as compared to patients treated with etanercept. *See* Wallis et al. (2004), *Clin. Infect. Dis.* 38:1261-5 (Document D5 on SB/08 filed March 29, 2011).

None of the purported objections to Applicants' evidence of unexpected results have any relevance to whether the ordinary skilled person would have been motivated to select nucleic acids and methods of the claimed invention from among the multitude of possible species, subgenuses and genuses, or whether unexpected properties of the claimed invention render it nonobvious. The absence of an expected property, in this case lack of effector functions, should be considered evidence of nonobviousness. MPEP §§ 716.02(b)(III) and 716.02(a)(IV). Similarly, the presence of an unexpected property, *e.g.* an improvement in binding affinity, kinetic stability or neutralization activity, is evidence of nonobviousness.

B. Dembic in view of the Smith Patent and the Capon Patent

The Action attempts at page 18 to evade applicability of the Board's holding of nonobviousness, by merely adding the Smith patent as a third reference to the combination of Dembic and Capon. This express combination of references has already been considered by the Board and deemed insufficient to support a conclusion of obviousness. Decision, page 2. Maintaining this rejection only delays prosecution, which is expressly contrary to the Patent Office's policy of compact prosecution (see, e.g., MPEP §2106(II)).

C. Smith Patent, in view of Hohmann and the Capon Patent

Hohmann was cited merely for teaching that HL60 cells express p75 TNFR. Action, p. 20. Hohmann adds nothing to the obviousness rejection discussed immediately above. The arguments explained above thus apply equally to this rejection.

IV. Conclusion

The Office Action fails to articulate a reason for selecting the starting structure cited from the Smith Patent, and fails to articulate a reason to modify that structure when the Smith Patent explicitly teaches against modifying the constant region. In addition,

Applicants have submitted overwhelming, uncontradicted evidence showing that fusion proteins encoded by the claimed nucleic acids, or produced by the claimed methods, have unexpected properties in more than six different categories, such as TNFα binding and inhibition, FcγR-binding, C1q-binding, ADCC, CDC, aggregation ability and binding stoichiometry. Researchers in the art have opined that these unexpected properties have practical significance because they may be related to clinical functions. As with the previous rejection based on Dembic and Capon et al. that was overturned by the Board of Patent Appeals and Interferences in related U.S. Patent No. 8,063,182, Applicants' demonstration of unexpected results rebuts the outstanding obviousness rejection. Applicants respectfully request that the rejections be withdrawn and the instant claims proceed to issuance.

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Respectfully submitted,

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